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Long-term prognostic impact of CT-Leaman score in patients with non-obstructive CAD: Results from the COronary CT Angiography EvaluatioN For Clinical Outcomes InteRnational Multicenter (CONFIRM) study☆

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ABSTRACT

Background: Non-obstructive coronary artery disease (CAD) identified by coronary computed tomography angiography (CCTA) demonstrated prognostic value. CT-adapted Leaman score (CT-LeSc) showed to improve the prognostic stratification. Aim of the study was to evaluate the capability of CT-LeSc to assess long-term prognosis of patients with non-obstructive (CAD).
Methods: From 17 centers, we enrolled 2402 patients without prior CAD history who underwent CCTA that showed non-obstructive CAD and provided complete information on plaque composition. Patients were divided

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into a group without CAD and a group with non-obstructive CAD (<50% stenosis). Segment-involvement score (SIS) and CT-LeSc were calculated. Outcomes were non-fatal myocardial infarction (MI) and the combined end-point of MI and all-cause mortality.
Results: Patient mean age was 56 ± 12 years. At follow-up (mean 59.8 ± 13.9 months), 183 events occurred (53 MI, 99 all-cause deaths and 31 late revascularizations). CT-LeSc was the only multivariate predictor of MI (HRs 2.84 and 2.98 in two models with Framingham and risk factors, respectively) and of MI plus all-cause mortality (HR 2.48 and 1.94 in two models with Framingham and risk factors, respectively). This was confirmed by a net reclassification analysis confirming that the CT-LeSc was able to correctly reclassify a significant proportion of patients (cNRI 0.28 and 0.23 for MI and MI plus all-cause mortality, respectively) vs. baseline model, whereas SIS did not.
Conclusion: CT-LeSc is an independent predictor of major acute cardiac events, improving prognostic stratification of patients with non-obstructive CAD.

1. Introduction

In recent years, studies supporting the prognostic value of coronary CT angiography (CCTA), including single-center studies and a large multicenter registry, have been published [1,2]. According to these data, while the absence of identifiable plaques in the coronary tree is associated with an excellent prognosis, it has also been consistently demonstrated that the identification of non-obstructive lesions, a unique feature of CCTA as a non-invasive coronary imaging modality, has prognostic value. This has clinical implications because many patients fall in this category, as reflected by the high proportion of patients with atherosclerotic plaques in many CCTA databases [2–5]. Nevertheless, as non-obstructive CAD is a very heterogeneous and prevalent condition, there is the need for tools to quantify total coronary atherosclerotic burden in order to better stratify these patients. Recently, a new developed score, the CT-adapted Leaman score (CT-LeSc), using the comprehensive information on lesion localization, plaque composition and degree of stenosis provided by CCTA, resulted in a relatively small, single-center setting, to be an independent long-term predictor of hard cardiac events and to improve the CCTA prognostic stratification of non-obstructive CAD [6].

In the present prospective international multicenter study, we evaluated the capability of the CT-LeSc to stratify the long-term prognosis of a large cohort of patients with non-obstructive CAD at CCTA evaluation.

2. Methods

2.1. Study population

The design and rationale of the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) registry has been described previously [7]. For the current study, we utilized the data from the CONFIRM long-term follow-up registry that included only patients who had a follow-up duration of more than three years. Overall, 17,181 patients who underwent CCTA at 17 centers in 9 countries (Austria, Canada, Germany, Israel, Italy, Portugal, South Korea, Switzerland, and United States) were enrolled between February 2003 and May 2011 for long-term follow-up. Inclusion criteria were age >18 years, a CCTA performed with a scanner equipped with at least 64-detectors, and CCTA images of interpretable quality. Among the 5010 patients in whom MACE data at follow-up and complete plaque characteristics data were collected we excluded those with prior history of CAD ($n = 1741$), myocardial revascularization performed early after CCTA (<90 days) ($n = 377$) and presence of obstructive coronary lesions (>50%) ($n = 490$). The analytic sample comprised 2402. patients. Informed consent was obtained from each patient and [2] the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

2.2. Risk factor assessment

Clinical CAD risk factors including smoking, hypertension, dyslipidemia, diabetes, and family history were collected prior to CCTA examination by direct patient interview performed by a physician or nurse research coordinator and/or with standardized site questionnaires [7].

2.3. Imaging analysis

CCTA data were acquired using multi-detector row CT scanners consisting of 64-rows or greater. Expert readers analyzed all CCTA images according to the guidelines of the Society of Cardiovascular Computed Tomography (SCCT) [8,9]. We defined coronary atherosclerosis in CCTA images as any tissue structure larger than 1 mm^2, which was either within the lumen of the coronary artery or adjacent to the coronary artery lumen and could be distinguished from the adjacent epicardial fat, pericardial tissue, or the artery lumen. We used a modified American Heart Association 16-segment coronary artery tree model for analysis [10]. Coronary artery luminal narrowing was defined as the presence of any plaque resulting in a % diameter reduction >0. Non-obstructive lesions were defined as coronary artery segments showing plaques with a luminal diameter stenosis <50%. Normal CCTA was defined as the absence of any coronary artery luminal narrowing. The SIS, ranging from 0 to 16, was calculated as the total number of segments with plaques (any degree of stenosis). The methodology for the CT-LeSc has been previously described [11]. Briefly, three sets of weighting factors are used for this score: 1) localization of the coronary plaques, accounting for dominance; 2) type of plaque, with a multiplication factor of 1 for calcified plaques and of 1.5 for non-calcified and mixed plaques; and 3) degree of stenosis, with a multiplication factor of 0.615 for non-obstructive (<50% stenosis) and a multiplication factor of 1 for obstructive (≥50% stenosis) lesions. The CT-LeSc was calculated on a patient level as the sum of the partial CT-LeSc of all evaluable coronary segments. For both the SIS and the CT-LeSc, prognostically validated cut-off values (>5) were used [4,6]. Analysis of coronary artery calcium score was performed when available. The total mean dose length product for CCTA was estimated to be 938 ± 379 mGy × cm, corresponding to an estimated radiation dose of 13 ± 5 mSv.

2.4. Patient follow-up

The primary outcomes of the current study were non-fatal myocardial infarction (MI) and the combined end-point of MI and all-cause mortality. As previously reported [7], the outcomes were assessed at each institution by direct interview, telephone contact, review of medical records, or using a mailed standardized questionnaire. In the USA, all-cause mortality was additionally searched by the Social Security Death Index. Site physicians defined MI according to ACC/AHA guidelines and the World Health Organization Universal Definition of Myocardial Infarction [12]. All revascularizations were recorded and patients with elective myocardial revascularization were censored at follow-up.

2.5. Statistical analysis

Categorical variables are presented as counts and proportions. Continuous variables are presented as means ± SD. A one-way ANOVA or the Kruskal–Wallis test was used to conduct continuous variables intergroup comparisons among patients without CAD, non-obstructive CAD but a LS < 5 and non-obstructive CAD but a LS > 5. Pearson's chi-square test (χ^2) was used for categorical variables comparison. Time-to-event analysis for the study endpoints were calculated using univariable Cox proportional-hazards models reporting hazard ratios (HR) with 95% confidence intervals (95% CI). Multivariable Cox proportional hazards models were also constructed with variables based on clinical judgment univariate analysis results. All the analyses were performed evaluating combined endpoints (MI, MI plus all cause of death,). To avoid overfitting and multicollinearity issues, we developed four different models, for all different combined endpoints. The first model was adjusted for the CT-LeSc and the Framingham risk score. The second model was adjusted for the SIS and the Framingham risk score. The third model was adjusted for the CT-LeSc and baseline clinical characteristics. The fourth model was adjusted for the SIS and baseline clinical characteristics.

A sub-analysis were performed in patients in which CACS was available; a prognostically validated cut-off >400 was used as previously suggested [13]. Moreover we performed a separate sub-analysis for patients with and without chest pain at baseline. Of note, in the analysis of symptomatic subjects the Morise score was included in model 1 and 2, instead of the Framingham score.

Survival curves were calculated using the Kaplan–Meier method for population stratified by the presence of non-obstructive CAD and the CT-LeSc, with each survival curve compared using the log-rank test. A two-tailed p value of <0.05 was considered statistically significant. The comparison between performance of the CT-LeSc and SIS added to a baseline model was further quantified by a continuous net reclassification index (cNRI) [14].

3. Results

3.1. Patient characteristics and MACE

Indications for CCTA were chest pain (1200 patients, 49.9%), multiple CAD risk factors (595 patients, 24.7%), and equivocal or abnormal stress test results (607 patients, 25.3%). Mean pre-test probability of CAD was low-to-intermediate (mean Morise score 11.6 ± 4.2). The mean duration of follow-up was 59.8 ± 13.9 months, up to 96 months (Table 1). One-hundred and eighty-three patients exhibited events during follow-up (53 MI, 99 all-cause deaths and 31 late revascularizations).

3.2. Univariate predictors of events

Among clinical characteristics, therapy with aspirin was the only predictor of MI, whereas hypertension and diabetes were predictors of MI plus all-cause death. Among CCTA data, a SIS > 5 and non-obstructive CAD with a CT-LeSc > 5 were predictors of MI, whereas a SIS > 5, non-obstructive CAD with a CT-LeSc ≤ 5 and non-obstructive CAD with a CT-LeSc > 5 were predictors of MI plus all-cause death (Table 2).

3.3. Multivariate predictors of events

The only significant independent predictor of MI was non-obstructive CAD with a CT-LeSc > 5 (HR 2.84 and 2.98 in model 1 and model 3, respectively). The independent predictors of MI plus all-cause death were the Framingham score (HR 1.02 and 1.03 in model 1 and model 2, respectively), age (HR 1.04 and 1.05 in model 3 and model 4, respectively), diabetes (HR 1.84 and 1.86 in model 3 and model 4, respectively), a SIS > 5 (HR 1.95 in model 2, HR not significant in model 4), non-obstructive CAD with a CT-LeSc ≤ 5 (HR 2.05 and 1.55 in model 1 and model 3, respectively) and non-obstructive CAD with a CT-LeSc > 5 (HR 2.48 and 1.94 in model 1 and model 3, respectively) (Table 3).

Table 1
Clinical and CCTA baseline characteristics.

	All patients (n = 2402)	No CAD (n = 1450)	Non-obstructive CAD with LS ≤ 5 (n = 611)	Non-obstructive CAD with LS > 5 (n = 341)
Clinical characteristics				
Age	56 ± 12	53 ± 12	61 ± 10*	63 ± 11*,ς
Male	1208 (50.3)	657 (45.3)	346 (56.7)*	205 (60.1)*
BMI	28 ± 5.49	27.79 ± 5.39	28.09 ± 5.11	28.61 ± 6.40
Hypertension	1302 (54.2)	674 (46.5)	394 (64.5)*	234 (68.6)*
Diabetes	252 (10.5)	116 (8)	74 (12.1)§	62 (18.1)*,ς
Current smoking	425 (17.7)	250 (17.2)	105 (17,2)	70 (20.53)
Family history	798 (33.2)	492 (33.9)	188 (30,8)	118 (34.6)
Dyslipidemia	1207 (50.3)	641 (44.2)	342 (56)*	224 (65.7)*,ς
Morise	11.57 ± 4.16	10.70 ± 4.42	12.68 ± 3.37*	13.19 ± 3.31*
Framingham	11.99 ± 9.63	9.74 ± 7.78	14.83 ± 10.46*	16.27 ± 11.98*
Chest pain at baseline				
No chest pain	1053 (43.8)	590 (40.7)	308 (50.4)	155 (45.4)
Non-cardiac/unspecified pain	418 (17.4)	296 (20.4)	79 (12.9)	43 (12.6)
Atypical chest pain	737 (30.7)	436 (30.1)	184 (30.1)	117 (34.3)
Typical chest pain	194 (8.1)	128 (8.8)	40 (6.5)	26 (7.6)
Therapy				
ASA	503 (20.9)	265 (18.3)	137 (22.4)§	101 (29.6)*,ς
Statin	506 (21.1)	226(15.6)	161 (26.4)*	119 (34.8)*,ς
CCTA characteristics				
SIS	1.08 ± 1.89	0	1.61 ± 0.88*	4.64 ± 2.36*,o

Continuous variable are expressed as mean ± SD; Ordinal variables are expressed as n (%); BMI: body mass index; SIS: segment involvement score; LS: Leaman score; CAD: coronary artery disease.

* p < 0,0001 vs no CAD.
o p < 0,0001 vs LS < 5.
§ p < 0,05 vs no CAD.
ς p < 0,05 vs LS < 5.

Table 2
Univariate analysis.

	MI	MI + all-cause death		
	HR (95% CI)	*p*	HR (95% CI)	*p*
Clinical characteristics				
Age	1 (0.98–1.02)	0.871	1.04 (1.02–1.05)	<0.0001
Male	0.78 (0.46–1.32)	0.343	1.1 (0.79–1.51)	0.5731
BMI	1.03 (0.99–1.07)	0.128	1.01 (0.98–1.04)	0.596
Hypertension	1.52 (0.87–2.67)	0.143	1.97 (1.39–2.79)	<0.0001
Diabetes	1.85 (0.9–3.79)	0.095	1.95 (1.29–2.96)	0.002
Current smoking	1.68 (0.91–3.1)	0.096	1.33 (0.91–1.95)	0.144
Family history	1.46 (0.84–2.52)	0.182	0.86 (0.1–1.23)	0.417
Dyslipidemia	1.17 (0.68–2.01)	0.573	0.9 (0.65–1.24)	0.505
Morise	0.98 (0.92–1.05)	0.629	1.03 (0.99–1.07)	0.168
Framingham	1.01 (0.99–104)	0.366	1.03 (1.02–1.04)	<0.0001
Chest pain at baseline				
No chest pain	1		1	
Non-cardiac pain/unspecified	1.34 (0.69–2.64)	0.388	0.80 (0.52–1.24)	0.325
Atypical chest pain	0.82 (0.42–1.57)	0.547	0.50 (0.33–0.75)	0.001
Typical chest pain	1.07 (0.41–2.80)	0.886	0.60 (0.31–1.16)	0.130
Therapy				
ASA	1.84 (1.01–3.34)	0.046	1.42 (0.98–2.05)	0.063
Statin	1.2 (0.63–2.27)	0.585	1.12 (0.77–1.63)	0.563
CCTA characteristics				
SIS > 5	1.13 (1.02–1.26)	0.022	1.18 (1.12–1.25)	<0.001
No CAD	1		1	
Non-Ob CT-LeSc ≤ 5	1.18 (0.62–2.23)	0.618	1.88 (1.3–2.72)	0.0008
Non-OB CT-LeSc > 5	2.11 (1.11–3.99)	0.023	2.37 (1.58–3.57)	<0.001

BMI: body mass index; SIS: segment involvement score; CT-LeSc: CT-Adapted Leaman Score; Non-Ob: non-obstructive coronary artery disease (stenosis < 50%); MI: non-fatal myocardial infarction; CAD: coronary artery disease.

Table 3
Multivariate analysis.

	MI		MI + all-cause death	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Model 1				
Framingham	1.01 (0.98–1.04)	0.4316	1.02 (1.01–1.04)	0.0006
ASA	1.51 (0.82–2.77)	0.1860	1.32 (0.91–1.93)	0.1402
Non-Ob CT-LeSc < 5	1.70 (0.84–3.47)	0.1444	2.05 (1.36–3.01)	0.0006
Non-Ob CT-LeSc > 5	2.84 (1.38–5.85)	0.0049	2.48 (1.58–3.90)	0.0001
Model 2				
ASA	1.67 (0.91–3.05)	0.0995	1.41 (0.98–2.06)	0.0672
Framingham	1.02 (0.99–1.05)	0.1011	1.03 (1.02–1.04)	<0.0001
SIS > 5	0.85 (0.20–3.35)	0.8252	1.95 (1.09–3.49)	0.0244
Model 3				
Age	0.99 (0.96–1.02)	0.7768	1.04 (1.02–1.06)	<0.0001
Male	0.67 (0.35–1.28)	0.2363	0.91 (0.62–1.34)	0.6515
BMI	0.98 (0.93–1.04)	0.6053	0.99 (0.95–1.02)	0.6837
Hypertension	1.13 (0.57–2.26)	0.7140	1.39 (0.89–2.14)	0.1414
Diabetes	1.41 (0.60–3.32)	0.4242	1.84 (1.13–2.99)	0.0138
Current smoking	1.11 (0.50–2.43)	0.7914	1.42 (0.89–2.26)	0.1342
Dyslipidemia	1.10 (0.57–2.11)	0.7719	0.74 (0.50–1.09)	0.1342
Family history	1.23 (0.65–2.31)	0.5184	1.06 (0.71–1.59)	0.7598
ASA	1.42 (0.73–2.76)	0.2937	1.08 (0.71–1.65)	0.6983
Non-Ob CT-LeSc < 5	1.64 (0.73–3.65)	0.2252	1.55 (0.97–2.45)	0.0627
Non-Ob CT-LeSc > 5	2.98 (1.35–6.58)	0.0070	1.94 (1.18–3.12)	0.0095
Model 4				
Age	1.01 (0.98–1.03)	0.5466	1.05 (1.03–1.07)	<0.0001
Male	0.79 (0.42–1.49)	0.4813	0.99 (0.68–1.46)	0.9953
BMI	0.98 (0.93–1.04)	0.7247	0.99 (0.95–1.03)	0.7503
Hypertension	1.19 (0.59–2.37)	0.6170	1.46 (0.94–2.25)	0.0900
Diabetes	1.52 (0.65–3.55)	0.3278	1.86 (1.14–3.02)	0.0125
Current smoking	1.20 (0.55–2.64)	0.6413	1.49 (0.93–2.35)	0.0957
Dyslipidemia	1.21 (0.63–2.32)	0.5568	0.77 (0.52–1.13)	0.1878
Family history	1.28 (0.68–2.39)	0.4402	1.08 (0.72–1.61)	0.7032
ASA	1.54 (0.79–2.96)	0.2001	1.13 (0.74–1.72)	0.5560
SIS > 5	0.83 (0.19–3.52)	0.8043	1.38 (0.74–2.56)	0.3083

3.4. Survival analysis

When MI only was considered as outcome, the event-free survival rates were 98% in patients without CAD, 98% in patients with non-obstructive CAD and a CT-LeSc ≤ 5 and 95% in patients with non-obstructive CAD and a CT-LeSc > 5 (log-rank p value = 0.01) (Figure 1A). When the end-point of MI plus all-cause mortality was used, event-free survival rates were 97%, 92% and 88% in patients without CAD, with non-obstructive CAD and a CT-LeSc ≤ 5 and with non-obstructive CAD and a CT-LeSc > 5, respectively (log-rank p value < 0.0001) (Figure 1B).

3.5. Reclassification index

The net reclassification analysis (Table 4) showed that a CT-LeSc > 5 is able to correctly reclassify a significant proportion of patients (0.28 and 0.23for MI and MI plus all-cause mortality, respectively), in comparison with the baseline model including age, male gender, diabetes, hypertension, smoking, dyslipidemia, and family history of premature CAD. Conversely, reclassification using a SIS > 5 was not statistically significant in any models.

3.6. Coronary artery calcium score sub-analysis

Coronary artery calcium score (CACS) was available in 1537 patients (64%). CACS > 400 was identified in 67 patients (4.4%) in the entire cohort; CACS > 400 was present in 6 patients (1.6%) with CT LeSc ≤ 5 and in 61 subjects (22.9%) among those with CT LeSc > 5. At univariate analysis neither CACS > 400 or SIS > 5 was associated with MI (HR 1.85; 95% CI 0.57–5.98, $p = 0.306$ and 0.89; 0.22–3.68, $p = 0.896$), while only CT-LeSc > 5 was a significantly predictors of MI (HR 2.09; 95% CI 1.02–4.30, $p = 0.04$). When the composite endpoint including MI and all cause of death was considered, CACS > 400, SIS > 5 and CT-LeSc > 5

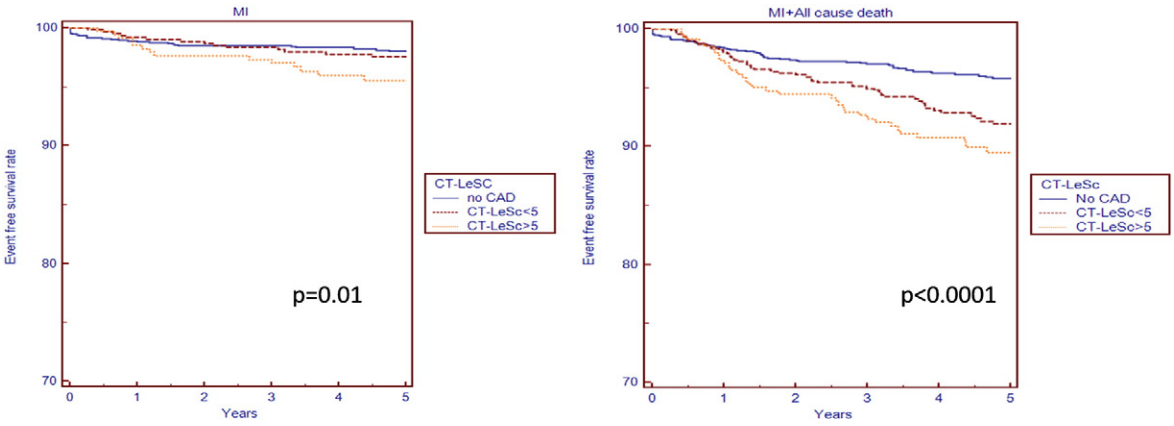

Fig. 1. Kaplan-Meier survival curves for MI (A) showing the event-free survival rates of 98% in patients with non-obstructive CAD and a CT-LeSc ≤ 5 and 95% in patients with non-obstructive CAD and a CT-LeSc > 5 (log-rank *p* value = 0.01). When the end point was MI plus all-cause mortality (B), event-free survival rates were 97%, 92% and 88% in patients without CAD, with non-obstructive CAD and a CT-LeSc ≤ 5 and with non-obstructive CAD and a CT-LeSc > 5, respectively (log-rank *p* value < 0.0001). MI: myocardial infarction; CAD: coronary artery disease; CT-LeSc: computed tomography adapted Leaman score.

were all significative predictors of events (HR 3.99, HR 2.38 and HR 2.73, respectively; $p < 0.001$).

At multivariate analysis CACS > 400 remains a significantly predictor of MI + all cause of death when adjusted for Framingham risk score (HR 3.04; 95% CI 1.72–5.36, $p < 0.001$) and for baseline clinical characteristics (HR 2.05; 95% CI 1.14–3.68, $p = 0.017$); SIS > 5 remains significantly associated to MI + all cause of death only when adjusted for Framingham risk score (HR 1.96; 95% CI 1.09–3.55, $p = 0.027$), but not when adjusted for clinical baseline characteristics.

Of note, only CT-LeSc > 5 was significantly associated to MI when adjusted both for Framingham risk score (HR 2.68; 95% CI 1.18–6.12, $p = 0.019$) and for baseline clinical characteristics (HR 3.13; 95% CI 1.29–7.53, $p = 0.012$) at multivariate analysis. When the composite endpoint including MI + all cause of death was considered CL-LeSc > 5 was still associated to events both when adjusted for Framingham risk score (HR 2.52; 95% CI 1.52–4.16, $p < 0.001$) and for baseline characteristics (HR 1.79, 95% CI 1.05–3.05, $p = 0.038$).

In this subgroup of patients with CACS reported, the event free survival rates were 98% in those with CT-LeSc < 5 and 95% in those with CT-LeSc > 5 (log-rank $p = 0.0289$) (Figure 2B); on the contrary CACS > 400 score was not significantly associated to worst survival rates (Figure 2A).

3.7. Asymptomatic patients vs symptomatic patients

Among the entire cohort 1053 patients (43.8%) did not report chest pain at baseline, while 1349 patients (56.2%) were symptomatic at the time of CCTA.

A separate sub-analysis in asymptomatic subjects showed that at univariate analysis there were no predictor of MI; on the contrary, age, hypertension, diabetes and the Framingham score were the clinical characteristics associated to MI + all cause of death, while among CT parameters both SIS > 5 and CT-LeSc > 5 were associated to MI + all cause of death (Table 5).

Table 4
Net Reclassification Index for SIS > 5 and CT-LeSc > 5 for prediction of composite endpoints.

	MI			MI + all-cause death		
	cNRI	cNRI 95% CI	*p*	cNRI	cNRI 95% CI	*p*
BL	—	—	—	—	—	—
BL + SIS > 5	0.15	−0.09–0.40	0.271	−0.039	−0.19–0.11	0.648
BL + CT-LeSc > 5	0.28	0.02–0.54	0.046	0.23	0.07–0.39	0.006

In the subgroups of patients with chest pain at baseline only CT-LeSc > 5 was associated to MI at univariate (HR 2.5; 95% CI 1.13–5.75, $p = 0.025$), while age, hypertension and the Morise score were associated to MI + all cause of death, but only CT-LeSc > 5 (HR 2.53; 95% CI 1.42–4.48, $p = 0.002$) was found to be associated to this composite end-point among CCTA variables (Table 6).

At multivariate analysis SIS > 5 was not associated to endpoints both in asymptomatic and symptomatic patients. On the contrary CT-LeSc > 5 was found to be a predictor of MI in symptomatic patients (HR 2.63 and 2.76 in Model 1 and 3, respectively) and to be associated with MI + All cause of death both in asymptomatic and symptomatic patients only when adjusted for Framingham or Morise score (HR 2.56 and 2.39 in asymptomatic and symptomatic patients, respectively), but not when clinical baseline characteristics were evaluated separately (Table 7).

4. Discussion

Coronary CTA has been demonstrated to be accurate for the detection of non-obstructive CAD and coronary atherosclerosis when compared to coronary intravascular ultrasound [15]. Detection of non-obstructive CAD, which may be considered an unique feature of CCTA among other non-invasive imaging modalities, has relevant prognostic implications. Indeed, it may identify a population that has an higher event-free survival rate as compared to that of patients with obstructive disease but lower than that of patients with normal coronaries [4,5,16,17]. In order to better stratify the prognosis among the large and heterogeneous cohort of patients with non-obstructive CAD, different coronary plaque scores have been proposed. Among them, the SIS and SSS demonstrated a remarkable prognostic value [4,18]. Particularly, a single-center study by Bittencourt et al. demonstrated that among patients with obstructive CAD, a greater extent of non-obstructive plaques, as quantified by SIS, was associated with a higher event rate [16].

4.1. CT adapted-Leaman score

A recently proposed plaque score, the CT-LeSc based on lesion localization, plaque composition and degree of stenosis, demonstrated to improve the prognostic stratification of non-obstructive CAD in an another single-center study [6]. To the best of our knowledge, this is the first prospective international multicenter study finalized to evaluate if the CT-LeSc is able to stratify the long-term prognosis in a selected but large patient cohort with non-obstructive lesions. The main findings of the study are that the CT-LeSc allows to distinguish within patients with non-obstructive CAD those with a cardiac event risk similar to that shared by patients without plaques from those with a less favorable

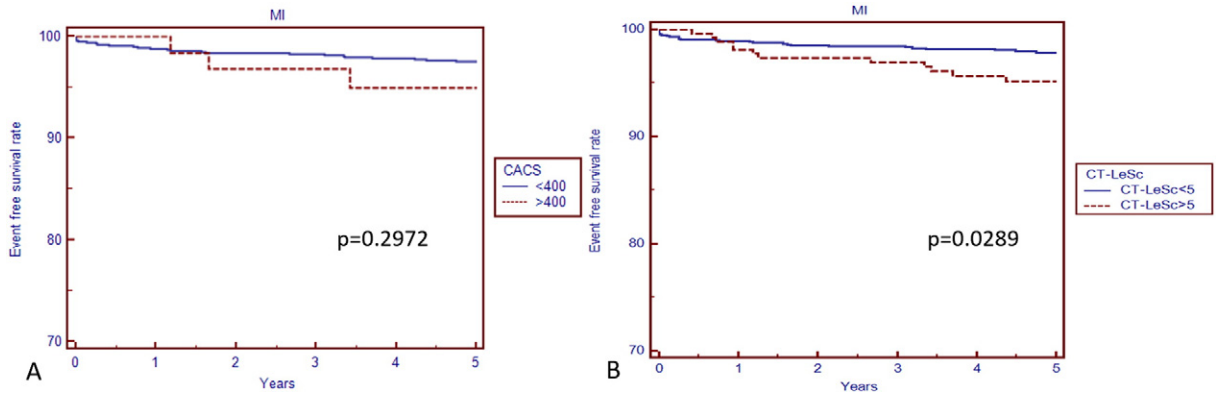

Fig. 2. Kaplan Meyer survival curves for MI using CACS (A) and CT-LeSc (B). CACS > 400 was not able to stratify patients at higher risk of MI. On the contrary, patients with CT-LeSc > 5 was associated to an event free survival rate of 95%, that was found to be significantly lower than patients with CT-LeSc < 5 (log-rank $p = 0.0289$). MI: myocardial infarction; CACS: coronary artery calcium score; CT-LeSc: computed tomography adapted Leaman score.

prognosis. Moreover, the CT-LeSc appears to be superior to the SIS, despite the latter already showed to possess a good prognostic value. In particular, analyzing the primary outcomes of the study we found that a CT-LeSc > 5 was an univariate predictor of MI and MI plus all-cause death and the only multivariate predictor of MI.

4.2. CT-LeSc vs SIS

The CT-LeSc appears to be superior to the SIS that exhibited HR systematically lower than the CT-LeSc at both univariate and multivariate analysis. This is confirmed by the net reclassification analysis showing that the CT-LeSc, but not the SIS, was able to correctly reclassify a significant proportion of patients vs. a baseline model including age, gender and risk factors for both primary and secondary endpoints.

4.3. CACS and CT-LeSc

In the sub-group of patients with calcium score, CACS > 400 has been confirmed to be a predictor of composite end-point including all cause of death, but only CT-LeSc appeared to correctly identify patients at higher risk of MI. These findings could be explained by recent studies, suggesting that non-calcified plaques may be associated to higher risk of acute coronary syndrome when compared to calcified ones [19].

4.4. Asymptomatic and symptomatic patients

Approximately half of the patients included in this study were asymptomatic for chest pain at the time of CCTA. In order to better clarify the possible role of CCTA in the evaluation of asymptomatic patients we performed a specific separate analysis in asymptomatic vs symptomatic patients. Of note we have found no clinical or CCTA parameters resulting to be significantly associated to MI in asymptomatic patients. On the contrary in symptomatic patients only CT-LeSc > 5 was associated to MI both at univariate and multivariate analyses. This findings suggest that CT-LeSc could be an important tool to discriminate patients at higher risk of MI among those symptomatic for chest pain, even if CCTA results to be negative for significative stenosis (>50%).

4.5. Survival analysis

Analyzing the survival curves for primary endpoints, we found that MI-free survival rate was 98% for patients with normal coronary arteries and for those with non-obstructive CAD and a CT-LeSc ≤ 5. Conversely, the survival rate fell to 95% in the presence of a CT-LeSc > 5, confirming the power of the CT-LeSc in stratifying the prognosis of patients with non-obstructive lesions. Adding all-cause mortality to MI in the survival analysis, patients with non-obstructive stenosis and a low CT-LeSc

Table 5
Univariate analysis for asymptomatic patients.

	MI	MI + all-cause death		
	HR (95% CI)	*p*	HR (95% CI)	*p*
Clinical characteristics				
Age	1.01 (0.98–1.04)	0.578	1.03 (1.01–1.05)	0.001
Male	0.68 (0.31–1.52)	0.356	0.93 (0.60–1.43)	0.717
BMI	1.04 (0.98–1.09)	0.182	1.02 (0.98–1.05)	0.424
Hypertension	1.63 (0.70–3.78)	0.261	1.83 (1.15–2.94)	0.011
Diabetes	1.43 (0.43–4.79)	0.556	2.05 (1.15–3.63)	0.015
Current smoking	0.99 (0.34–2.89)	0.996	0.98 (0.55–1.75)	0.962
Family history	1.26 (0.54–2.93)	0.597	0.77 (0.46–1.29)	0.333
Dyslipidemia	0.62 (0.27–1.42)	0.263	0.67 (0.40–1.01)	0.052
Framingham	0.98 (0.93–1.03)	0.404	1.02 (1.01–1.03)	0.048
Therapy				
ASA	1.50 (0.56–3.99)	0.411	1.69 (1.03–2.77)	0.038
Statin	0.70 (0.20–2.40)	0.572	0.97 (0.55–1.72)	0.931
CCTA characteristics				
No CAD	1		1	
SIS > 5	1.94 (0.46–8.22)	0.367	2.02 (1.06–4.56)	0.034
Non-Ob CT-LeSc ≤ 5	1.12 (0.44–2.85)	0.807	2.11 (1.29–3.42)	0.003
Non-OB CT-LeSc > 5	1.61 (0.56–4.53)	0.376	2.17 (1.22–3.86)	0.009

Table 6
Univariate analysis for symptomatic patients.

	MI	MI + All-cause death		
	HR (95% CI)	*p*	HR (95% CI)	*p*
Clinical characteristics				
Age	1.01 (0.97–1.03)	0.921	1.04 (1.02–1.07)	<0.001
Male	0.86 (0.43–1.74)	0.862	0.74 (0.46–1.22)	0.246
BMI	1.02 (0.95–1.08)	0.641	1.01 (0.96–1.05)	0.754
Hypertension	1.15 (0.57–2.31)	0.696	1.76 (1.06–2.95)	0.031
Diabetes	1.93 (0.9–4.67)	0.149	1.83 (0.98–3.42)	0.059
Current smoking	1.49 (0.67–3.32)	0.323	1.39 (0.79–2.44)	0.249
Family history	1.38 (0.68–2.79)	0.373	1.05 (0.63–1.72)	0.866
Dyslipidemia	1.51 (0.74–3.08)	0.259	1.40 (0.87–2.29)	0.181
Morise	1.01 (0.92–1.09)	0.946	1.08 (1.02–1.16)	0.016
Therapy				
ASA	1.82 (0.84–3.93)	0.129	1.18 (0.66–2.08)	0.571
Statin	1.31 (0.59–2.87)	0.513	1.29 (0.76–2.18)	0.354
CCTA characteristics				
No CAD	1		1	
SIS	–	–	2.03 (1.01–5.31)	0.051
Non-Ob CT-LeSc ≤ 5	1.20 (0.49–2.92)	0.677	1.43 (0.80–2.57)	0.229
Non-OB CT-LeSc > 5	2.54 (1.13–5.75)	0.025	2.53 (1.42–4.48)	0.002

Table 7
Multivariate analysis for asymptomatic and asymptomatic patients.

	MI HR (95% CI)	p	MI + all-cause death HR (95% CI)	p
Asymptomatic patients				
Model 1*				
Non-Ob CT-LeSc > 5	3.34 (0.97–11.44)	0.059	2.56 (1.31–4.99)	0.006
Model 2*				
SIS > 5	2.42 (0.55–10.73)	0.248	1.80 (0.82–3.95)	0.144
Model 3§				
Non-Ob CT-LeSc > 5	3.15 (0.84–11.78)	0.089	1.50 (0.73–2.94)	0.227
Model 4§				
SIS > 5	1.19 (0.26–5.51)	0.821	0.98 (0.41–2.35)	0.967
Symptomatic patients				
Model 1#				
Non-Ob CT-LeSc > 5	2.63 (1.07–6.46)	0.035	2.39 (1.29–4.42)	0.006
Model 2#				
SIS > 5	–	–	2.03 (0.85–4.82)	0.110
Model 3§				
Non-Ob CT-LeSc > 5	2.76 (1.06–7.25)	0.040	1.81 (0.94–3.51)	0.075
Model 4§				
SIS > 5	–	–	1.54 (0.64–1.86)	0.807

§ Adjusted for ASA and baseline clinical characteristics.
# Adjusted for ASA and Morise score.
* Adjusted for ASA and Framingham score.

exhibited a prognosis that was halfway between that of patients without plaques and that of patients with a CT-LeSc > 5.

4.6. Future strategies for early detection of non-obstructive CAD

Previous studies have proposed that early identification of non-obstructive CAD with CCTA may lead to a more aggressive strategy to control cardiovascular risk factors and to improve clinical follow-up [4,20]. Recently, a sub-study of CONFIRM performed in a cohort of patients receiving baseline statin and aspirin treatment showed that statin therapy was associated with a significant mortality reduction in patients with non-obstructive CAD but had no impact on patients without CAD [18]. These are valid arguments in support of the identification of parameters, such as the CT-LeSc allowing to stratify the long-term prognosis of the large and heterogeneous group of patients in whom CCTA shows non-obstructive CAD. Moreover, recent studies demonstrated the prognostic value of plaque characterization by CCTA. Indeed, this non-invasive imaging modality is able to identify some features, such as vessel positive remodeling and low-attenuation plaques, that have been associated with a higher risk of cardiac events [19]. High-risk plaques can be detected by CCTA and are independent predictors of fatal and non-fatal acute coronary syndrome, while positive remodeling has been observed in coronary stenoses that, regardless of the degree of narrowing, were found to be functionally important by invasive fractional flow reserve [21]. Therefore, additional studies are needed to integrate the CT-LeSc with other features such as positive remodeling or eventually with non-invasive FFR by CCTA for improving the prognostic characterization of patients without obstructive coronary lesions.

4.7. Study limitations

In interpreting these data some limitations should be considered. First, management decisions in all patient, such as medical therapies or revascularization, were left to the discretion of the referring physicians. Because some therapies (i.e. aspirin, statin) may have a positive effect on patient outcomes and were commonly used in patients with and without plaques, we expect that differences between subgroups would be even greater in the absence of such treatments. Second, we included all-cause mortality in the primary and secondary endpoints given its unparalleled clinical importance and freedom from ascertainment bias. However, as specific causes of death for each patient were not uniformly available at all sites, the true proportion of deaths that could attributable to cardiovascular events in our patients is unknown. Third, this study included a cohort of patients who were referred for CCTA because of suspected CAD and were often symptomatic. Although it is unlikely that our patient symptoms were related to non-obstructive CAD, generalization of this study findings to asymptomatic patients remains uncertain. Fourth, data on coronary calcium score were not included in the analysis because they were available for two third only of the study population.

5. Conclusion

The CT-adapted Leaman score is an independent predictor of major acute cardiac events and allows to distinguish, among a population with non-obstructive CAD, patients with risk of cardiac events similar to those without plaques from patients with a less favorable prognosis.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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